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## Plasma volume expansion in early-onset hypertensive disorders of pregnancy Preeclampsia Eclampsia TRial Amsterdam (PETRA)

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Summary



## Summary

This thesis reports the effect of plasma volume expansion in the management of severe early-onset hypertensive disorders of pregnancy. Theoretical advantages and practical disadvantages are tested on maternal and fetal / neonatal outcome parameters. The **P**reeclampsia **E**clampsia **T**rial **A**msterdam (**PETRA**) enrolled 216 patients with severe and early-onset hypertensive disorders of pregnancy between April 1, 2000 and May 31, 2003.

In the introduction the current knowledge on the effects of iatrogenic manipulation of plasma volume is outlined. An elaborate overview of the choices and strategies within the trial is presented. Chapters 2-4 compare the primary and secondary endpoints between the randomization groups. Chapters 5-10 present post-hoc analysis of disease characteristics as observed in the PETRA-study. Chapters 11-13 present supplementary studies on the physiological effect of plasma volume expansion.

In **chapter 1** we present an overview of the literature regarding (a) plasma volume regulation and blood pressure control mechanisms outside pregnancy, (b) the changes in normal pregnancies and (c) the changes in pregnancies complicated by hypertensive disorders. In hypertensive disorders of pregnancy a vasoconstrictive state is present with low plasma volume, low cardiac output, high blood pressure and high systemic vascular resistance. Signs and symptoms are proteinuria, the hemolysis elevated liver enzymes low platelets (HELLP) syndrome, physical complaints and eclampsia. Therapeutic counteraction of low circulating volume by plasma expanders is presented as a subject of considerable controversy.

**Chapter 2** reports the influence of PVE on the primary outcome of the study, i.e. neonatal neurological development at term age (Prechtl score), and on perinatal death, neonatal morbidity and maternal morbidity. Although a trend towards less prolongation of pregnancy was observed in the treatment group, neonatal neurological development, morbidity and mortality did not differ. Total fetal and postnatal loss was 18%. One-hundred-twenty-seven children had a normal score on neurological examination at term age and eleven children had an abnormal score. Major maternal morbidity was equally distributed among groups and all maternal morbidity appeared reversible.

In **chapter 3** the effect of plasma volume expansion on pulsatility indices of the fetal umbilical and middle cerebral arteries in the PETRA study is reported. A series of measurements performed at admission, after 16 to 48 hours, 60 to 120 hours and 7 to 11 days was analyzed. Although treatment group patients received per protocol higher amounts of intravenous fluids resulting in a significant decrease in hemoglobin

count, the pulsatility indices in the umbilical artery and median cerebral artery did not differ between the treatment and control group at least during the first 7-11 days. We conclude that PVE had no effect on the fetal hemodynamics as measured by Doppler flow velocity parameters.

At one year post term no differences in infant outcome were observed between randomization groups (**chapter 4**). The Bayley development test was performed on 171 children out of 178 alive. The mean of MDI and PDI scores were low (88 [59-123] and 80 [50-118] respectively), but there was no difference in MDI or in PDI between the groups. In both groups a normal distribution of Bayley scores was found. In logistic regression analysis, fetal indication for delivery was the only factor predicting an abnormal MDI. Caucasian ethnicity and low birth weight were the only factors predicting an abnormal PDI.

In **chapter 5** the psychosocial impact of severe hypertensive disorders in pregnancy was studied. The 90 item Symptom Checklist was administered at three different test moments: term age, 3 months post term and 1 year post term. A high psychological impact was found, especially when gestational age at onset of disease is below 30 weeks or when adverse infant outcome occurs. However, psychosocial impact decreased over time in all women. In multivariate analysis gestational age at inclusion was the single relevant parameter related to SCL-90 score ('the earlier the worse'). One year post term 87% of women who, at inclusion, had expressed the intention to resume work after pregnancy, had actually resumed work. Nine percent were still on sick-leave.

**Chapter 6** explores the association between clinical parameters at admission and the subsequent development of major maternal complications or adverse infant outcome. The association with age, parity, ethnicity, body mass index, gestational age, estimated fetal weight, blood pressure, antihypertensive medication, pulse rate, hemoglobin concentration, admitting center, diagnosis at inclusion, chronic hypertension, and thrombophilia was explored by logistic regression analysis. Adverse infant outcome was predominantly influenced by gestational age (odds ratio 0.4 per week increment). Major maternal complications were correlated to multiparity (odds ratio 0.4) and estimated fetal weight (odds ratio 0.9 per 100 g increment). It was concluded that prediction at admission of the clinical course of the disease and the development of additional maternal complications was not feasible.

**Chapter 7** describes the variable disease expression and the patterns of development of major maternal morbidity and HELLP syndrome in women with different subtypes of hypertensive disorders of pregnancy. As in this cohort of patients the strategy aims at prolongation of pregnancy, the 'almost natural history' of the disease is captured.



The median time to delivery or fetal death was 8.2 (range 0.1-44) days. At study entry, 56 women (26%) had more than one diagnosis; this increased to 171 women (79%) by the time of discharge. The incidence of major maternal morbidity (total 26) was 4.2% at 2-4 days after inclusion and a mean of 1.7% (range 0-2%) thereafter per time frame of 3 days. The mean incidence of new or recurrent HELLP syndrome episodes was 5.5% (range 1.9-8.7%) per time frame of 3 days during the first 3 weeks after inclusion. Preeclampsia appeared to be a dynamic disease, with extensive overlap of subtypes of the syndrome. Prolongation of pregnancy in early-onset hypertensive disorders results in the development of further HELLP syndrome episodes and reversible major maternal morbidity but may improve perinatal healthy survival.

**Chapter 8** investigated the association of thrombophilic disorders with specific subtypes of hypertensive disorders of pregnancy. Three months post term, all patients were invited for a thrombophilia screening protocol. In this population, the high prevalence of thrombophilic factors and chronic hypertension was confirmed. In 75 patients (36%) a thrombophilic disorder was observed, 19 patients (9%) had more than two. Chronic hypertension was present in 32%, and 34% had a positive family history of cardiovascular morbidity. Between groups of subtypes of hypertensive disorders of pregnancy, there were small differences. In multinominal regression analysis hereditary thrombophilia was more frequent among women with infants with severe fetal growth restriction than in women with HELLP syndrome or severe preeclampsia.

The prevalence of abnormal General Movements in infants of the trial was reported in **chapter 9**. Relations between General Movements at term age and 3 months post term and neurological development at 3 months and 1 year post term were investigated. Definitely abnormal General Movements were observed in 10% at term age and in 13% at 3 months post term. Mildly abnormal in 36% and 40% respectively. Mildly or definitely abnormal General Movements at three months were not related to neurological examination at one year, but significantly related to the psychomotor developmental index. The high prevalence of mildly and definitely abnormal General Movements at term and three months and the absence of a relation to neurological examination at one year support the findings of others of the dynamic neurodevelopment over time. The delay in psychomotor development at one year stresses the need to combine various assessment techniques to identify infants at risk for affected neurodevelopmental outcome.

In **chapter 10** and **chapter 11** we explored a noninvasive method to measure hemodynamic changes during pregnancy.

In **chapter 10** the improved thoracic electrical bioimpedance technique to measure

cardiac output, stroke volume and systemic vascular resistance was evaluated. Nineteen healthy non-smoking women with an uncomplicated singleton pregnancy and no history of pre-existing vascular disorders participated in this study. During the second half of low-risk pregnancies significant individual and group trends could be determined (an increase in heart rate, a decrease in stroke volume, and an increase in systolic as well as diastolic blood pressure) by means of thoracic electrical bioimpedance with the random effects model.

The effect of plasma volume expansion on maternal hemodynamic parameters in early-onset hypertensive disorders of pregnancy was measured by means of thoracic electrical bioimpedance in **chapter 11**. Measurements were performed in 35 patients of the PETRA study group in the VUmc (16 managed with and 19 without plasma volume expansion). The mean values of measurements in the hypertension group were compared to the mean values of measurements between 24 and 32 weeks gestation in a group of 19 healthy low-risk pregnant women. As expected, a significant difference in heart rate, cardiac output and systemic vascular resistance was observed. Maternal hemodynamic parameters did not differ between patients managed with and without plasma volume expansion. A marginal decreased systemic vascular resistance was observed after plasma volume expansion.

